EIP PHARMA, INC

CLINICAL STUDY PROTOCOL

Title	A Phase 2b Clinical Study of the P38 Alpha Kinase Inhibitor Neflamapimod in Patients with Dementia with Lewy Bodies (DLB)
Investigational Product	Neflamapimod
Development Phase	2b
EIP Study Number	EIP21-NFD-504
IND Number	125198
NCT Number	NCT05869669
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Date (Version)	20 June 2023 (Version 2.0 Ex-US)
Sponsor Address	EIP Pharma, Inc. 20 Park Plaza, Suite 424 Boston, MA 02116 USA

CONFIDENTIAL

SPONSOR PROTOCOL APPROVAL PAGE

Signature

John J. Alam, MD

Sponsor Responsible Person

CEO, EIP Pharma Inc

Title

Date

INVESTIGATOR'S SIGNATURE OF AGREEMENT PAGE

I have read the protocol and, on behalf of my institution, agree to comply with all the conditions and instructions contained in this the protocol and with all applicable regulations.

Signature

Principal Investigator (printed name):

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Contract Research Organization:	Worldwide Clinical Trials
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Serious Adverse Event Reporting:	Worldwide Clinical Trials

SYNOPSIS

Study Title	A Phase 2b Clinical Study of the P38 Alpha Kinase Inhibitor Neflamapimod in Patients with Dementia with Lewy Bodies (DLB)
Protocol Number (date, Version)	EIP21-NFD-504 (Version 1.0 Ex-US, 03 March 2023)
Study Phase	2b
Study Centers	Approximately 30-40 study centers in the United States (US), Netherlands, and UK
Indication	Dementia with Lewy Bodies (DLB)
Study Objective	The primary objective is to demonstrate the efficacy of neflamapimod, compared to placebo, as a treatment for DLB, as assessed by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB). The secondary objectives are to: • Demonstrate that neflamapimod improves motor function in patients with DLB, compared to placebo, as assessed by the Timed Up and Go Test (TUG). • Demonstrate that neflamapimod improves cognition, compared to placebo, as assessed by a DLB-specific Neuropsychological Test Battery (NTB) in patients with DLB. The NTB is comprised of: o Cogstate Detection test (DET) o Cogstate Identification test (IDN) o Cogstate One Card Learning test (OCL) o Cogstate One Back test (ONB) o Letter Fluency Test • Demonstrate that neflamapimod improves global (cognition, function and behavior) disease status evaluated by a clinician with caregiver input, compared to placebo, in patients with DLB, as assessed by the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC).

Study Outcome Measures	Primary outcome measure: • Change in CDR-SB in neflamapimod treated-subjects compared to the placebo-treated subjects. Secondary outcome measures: • Change in TUG in neflamapimod-treated subjects compared to placebo-recipients. • Change in the composite score of the NTB, including tests of attention, executive function, and visual learning in neflamapimod-treated subjects compared to placebo-recipients. • ADCS-CGIC score at Week 16 in neflamapimod-treated subjects compared to placebo-recipients. As exploratory outcome measures, the effects of neflamapimod relative to placebo will be evaluated via changes in Dementia Cognitive Fluctuations Scale (DCFS); select domains of the 12-item Neuropsychiatric Inventory (NPI-12), including depression (dysphoria), apathy, hallucinations, and agitation/aggression; hallucinations frequency x severity score within the NPI-12 in subjects who report hallucinations at baseline; sleep and night-time behavior change within the NPI-12; MDS-UPDRS3 motor examination (Part III) score; beta functional connectivity and in alpha reactivity on quantitative EEG; and basal forebrain atrophy by structural MRI.
Number of Subjects	160 subjects are planned to be enrolled
Subject Population	Subjects aged ≥55 years with probable DLB by consensus criteria (McKeith et al, 2017), including a positive DaTscan™ and a CDR Global Score of 0.5 or 1.0. If the DaTscan is negative, but the subject has historical polysomnography (PSG)-verified REM sleep behavioral disorder (RBD), this will also qualify as probable DLB.
Inclusion Criteria	1. Men and women aged ≥55 years. 2. Subject is willing and able to provide written informed consent. 3. Probable DLB by consensus criteria (McKeith et al, 2017), including a positive DaTscan™. If the DaTscan is negative, but the subject has historical polysomnography (PSG)-verified REM sleep behavioral disorder (RBD), this will also qualify as probable DLB. 4. CDR Global Score less than 2.0 at Screening 5. If the patient is currently receiving cholinesterase inhibitor therapy, the patient must have received such therapy for greater than 3 months and on a stable dose for at least 6 weeks at the time of randomization. Except for reducing the dose for tolerability reasons, the dose of cholinesterase inhibitor may not be modified during the study. If the patient is not currently receiving cholinesterase inhibitor therapy, but received such therapy previously, that therapy must have been discontinued at least 3 months prior to randomization. Memantine therapy is allowed, if it had been started at least 3 months prior to randomization and the patient is also receiving cholinesterase inhibitor therapy (memantine monotherapy, i.e., without concomitant cholinesterase inhibitor therapy, is excluded).

	6. Normal or corrected eyesight and auditory abilities, sufficient to perform all aspects of the cognitive and functional assessments. 7. No history of learning difficulties that may interfere with their ability to complete the cognitive tests. 8. Received vaccination for SARS-CoV-19 unless medical contraindications prevent being vaccinated or has a history of natural infection. 9. Must have reliable informant or caregiver.
Exclusion criteria	1. Diagnosis of any other ongoing central nervous system (CNS) condition other than DLB, including, but not limited to, post-stroke dementia, vascular dementia, Alzheimer's disease (AD), or Parkinson's disease (PD). 2. Plasma ptau181 result above the threshold that indicates evidence of pathology associated with Alzheimer's disease at Screening. 3. Suicidality, defined as active suicidal thoughts within 6 months before Screening or at Baseline, defined as answering yes to items 4 or 5 on the C-SSRS, or history of suicide attempt in previous 2 years, or, in the Investigator's opinion, at serious risk of suicide. 4. Ongoing major and active psychiatric disorder and/or other concurrent medical condition that, in the opinion of the Investigator, might compromise safety and/or compliance with study requirements. 5. Diagnosis of alcohol or drug abuse within the previous 2 years. 6. Poorly controlled clinically significant medical illness, such as hypertension (blood pressure >180 mmHg systolic or 100 mmHg diastolic); myocardial infarction within 6 months; uncompensated congestive heart failure or other significant cardiovascular, pulmonary, renal, liver, infectious disease, immune disorder, or metabolic/endocrine disorders or other disease that would interfere with assessment of drug safety. 7. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio (INR) >1.5. 8. Known human immunodeficiency virus, hepatitis B, or active hepatitis C virus infection. 9. Participated in a study of an investigational drug less than six weeks or 5 half-lives of an investigational drug, whichever is longer, before enrollment in this study. 10. History of previous neurosurgery to the brain within the past five years. 11. If male with female partner(s) of child-bearing potential, unwilling or unable to adhere to contraception requirements specified in the protocol. 12. If female who has not has not reached menopause >1 year previously or has not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy, has a positive pregnancy test result during Screening and/or is unwilling or unable to adhere to the contraception requirements specified in the protocol.
Study Drug Details	Neflamapimod 40 mg capsule or matching placebo capsules.

Duration of Treatment	Screening window of 21 days (unless DaTscan is required, in which case Screening window may be extended to 35 days), 16 weeks of treatment, a 2-week follow-up visit for a total of up to 23 weeks of study participation. Subjects who complete the 16-week treatment phase will be offered the opportunity to continue in a 32-week open-label extension treatment. Based on the results of the double-blind treatment phase of the study, EIP Pharma will work with each country to provide access to treatment after completion of the extension phase, if there is a clear benefit.
Study Design and Methods	This is a Phase 2b (hypothesis-testing), multi-center, randomized, double-blind, placebo-controlled study of neflamapimod versus matching placebo (randomized 1:1) administered with food for 16 weeks in subjects with DLB. Subjects will receive 3 capsules per day (TID) with food (i.e., with the morning, mid-day and evening meals), of either neflamapimod 40 mg or placebo. Doses should be administered at least 3 hours apart. Following completion of informed consent procedures, subjects will enter the Screening phase of the study. One to two Screening visits are planned, during which safety screening measures will be undertaken as well as some cognitive assessments will be performed (per Schedule of Assessments). A plasma sample for pTau181 analysis will also be obtained at Screening and analyzed for eligibility purposes. Screening will be conducted within 21 days before Baseline (Day 1). If a DaTscan™ is required to determine study eligibility, Screening may be extended to 35 days. Once eligibility is confirmed, subjects will be stratified by background dementia therapy (one of three strata: no cholinesterase inhibitor therapy, cholinesterase inhibitor therapy alone, or cholinesterase inhibitor therapy plus memantine therapy) and randomly assigned on a 1:1 basis to neflamapimod 40mg TID or placebo for the 16-week treatment period. Investigators and subjects will be blinded to the treatment assignment. Dosing will start on Day 1 following completion of all baseline procedures. During the 16-week treatment period, subjects will return to the clinic every 2 weeks for the first month and then every 4 weeks thereafter. A Final Study Visit (i.e., Follow-Up Visit) will be conducted 2 weeks (+/-3 days) after completion of study drug or after the Early Termination (ET) visit. See the Schedule of Assessments for details regarding when assessments are conducted.
Therapy	Neflamapimod 40 mg capsules or matching placebo capsules will be administered orally TID with food for 16 weeks. Subject will receive matching (by size and color) capsules that contain either 40 mg neflamapimod or placebo. Subjects will be stratified by status of background dementia therapy (one of three strata: no cholinesterase inhibitor therapy, cholinesterase inhibitor therapy alone, or cholinesterase inhibitor therapy plus memantine therapy) and then randomized 1:1. Doses must be taken within 30 minutes following a meal or snack. Doses should be taken at approximately the same time each day throughout the study and at least 3 hours apart. Subjects completing the 16-week placebo-controlled main portion of the study will be offered an additional 32 weeks of neflamapimod treatment on an open-label basis.
Data and Safety Monitoring Board (DSMB)	There will be an independent Data and Safety Monitoring Board (DSMB) responsible for overseeing the safety of human subjects in this clinical trial. The DSMB will include at

	least three (3) members: two (2) clinicians with experience with dementia clinical trials, one of which will be the chair, and one (1) statistician. Members of the DSMB will be separate from members of the study team and site teams. The DSMB Charter will be reviewed and adopted by the DSMB; it will be a standalone document.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
APOE	Apolipoprotein E
APP	Amyloid-precursor-protein
AST	Aspartate aminotransferase
AUC	Area under the time concentration curve
BID	bis in die (twice a day)
CFT	Category Fluency Test
CIBIC-plus	Clinician Interview-Based Impression of Change, plus caregiver interview
CL	Clearance
CNS	Central nervous system
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
CYP	Cytochrome P450
DET	Cogstate Detection test
DLB	Dementia with Lewy Bodies
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early Termination
FDA	Food and Drug Administration
GAS	Goal Attainment Scale
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDN	Cogstate Identification Test

Abbreviation	Definition
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRT	Interactive Response Technology
LFT	Liver function test
MAP	Mitogen-activated protein
MAPKα	p38 mitogen activated protein kinase alpha
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
MWM	Morris-Water-Maze
NPI-12	12-item Neuropsychiatric Inventory
NTB	Neuropsychological Test Battery
OCL	Cogstate One Card Learning test
ONB	Cogstate One Back Test
p38α	Mitogen-activated protein kinase 14
PD	Parkinson's disease
PK	Pharmacokinetic
PSG	Polysomnography
pTau181	Phospho-tau 181
qEEG	Quantitative electroencephalography
RBD	REM sleep behavioral disorder
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SPECT	Single-photon emission computed tomography
TID	Three times daily
TUG	Timed Up and Go Test
ULN	Upper limit of normal
US	United States

1. INTRODUCTION

1.1. Scientific Rationale

This is a double-blind, placebo-controlled 16-week confirmatory (Phase 2b) treatment study of neflamapimod 40 mg administered 3 times daily (TID) in subjects with Dementia with Lewy Bodies (DLB). The primary objective of this study is to demonstrate the efficacy of neflamapimod, compared to placebo, as a treatment for DLB, as assessed by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB).

DLB is common, representing up to 15-20% of the dementia population, with an estimated 700,000 to one million affected individuals in the United States (US). There is evidence that the prognosis is even more severe than other dementia disorders, including Alzheimer's disease (AD). DLB is characterized by progressive dementia and fluctuating cognition (deficits in memory, attention), sleep disturbances, visual hallucination, and Parkinsonism (tremor, gait disturbance). See McKeith et al, 2017.

There are no treatments approved for the underlying disease process and only symptomatic treatments for parkinsonian symptoms. Although not approved for DLB, cholinesterase inhibitors provide modest improvement in cognitive function and reduce hallucination frequency, and as such a trial of cholinesterase inhibitor therapy is attempted in most patients. Despite the availability of treatment, patients with DLB have a greater rate of cognitive decline, incur higher healthcare costs, have longer hospitalizations, report lower quality of life, and have caregivers with higher levels of distress when compared with patients with AD (Mueller et al, 2017).

Neflamapimod is a highly specific inhibitor of the intra-cellular enzyme mitogen-activated protein kinase 14 (p38α). In the brain, p38α regulates inflammation through effects on microglia. Moreover, under conditions of stress and disease, p38α is also expressed in neurons and of the various p38 isoforms, the α isoform is the most important regulator of the stress response in neurons (Lawson et al, 2013). In the neuron, p38α also appears to play a critical role in inflammation-driven toxicity to synapses (Prieto et al, 2015). As a result of this understanding, p38 mitogen activated protein kinase alpha (MAPKα) has been recognized as a leading therapeutic target to improve synaptic function and synaptic plasticity for a broad range of central nervous system (CNS) disorders (Corrêa et al, 2012; Sandersen et al, 2016).

In the context of the major dementias, AD and DLB, emerging evidence indicates that the downstream pathological target of dysregulated p38α activation is a protein called Rab5. Rab5 is a major regulator of endocytosis and early endosomal function, and extensive scientific literature documents the critical roles of Rab5 in animal models of dementia (Nixon, 2017; Xu et al, 2018) with abnormal Rab5 activation leading to endolysosomal dysfunction, resulting in synaptic dysfunction, and with prolonged activation, neurodegeneration, particular with respect to cholinergic neurons (Pensalfini et al, 2020). As p38α is a known Rab5 activator and regulator of endosomal/endocytic function (Cavalli et al, 2001; Mace et al, 2005), neflamapimod was evaluated for activity against Rab5 activation. Neflamapimod treatment reversed Rab5+ endosomal enlargement *in vitro* in human Down Syndrome (DS) fibroblasts and *in vivo* in brain samples from an animal model of dementia (see Section 1.2 below).

Neflamapimod has been evaluated in DLB in an exploratory Phase 2a study (Jiang et al, 2022). This exploratory Phase 2a double-blind, placebo-controlled, parallel-group 16-week treatment study enrolled 91 patients with mild-to-moderate DLB (EIP19-NFD-501). As an exploratory (i.e., hypothesis-generating) study, no definitive conclusions regarding clinical efficacy could be inferred from the results.

However, neflamapimod demonstrated potential clinical activity on multiple clinical endpoints, which the current clinical study will attempt to confirm.

Briefly, Study 501 demonstrated a positive treatment effect on the primary outcome measure, with significant ($p<0.05$, linear mixed model for repeated measures, MMRM)), clinically relevant effect size improvement in cognition in subjects receiving 40mg neflamapimod three times daily (TID) compared to those receiving placebo as assessed by a Neuropsychological Test Battery (NTB; composed of 6 specific cognitive tests designed to assess attention and executive function). Significant positive treatment effects of 40mg TID neflamapimod relative to placebo were also seen on an Attention Composite that included tests within the NTB that measured information processing speed. Significant positive effects were not seen on either the NTB or on the attention composite, in the full efficacy population analysis, in which all patients receiving neflamapimod (including patients who received a lower dose of 40mg BID) were included in the analysis. However, significant positive treatment effects relative to placebo were seen in the full efficacy population analysis (i.e., including, those receiving neflamapimod TID or twice-daily) on cognition and function, as evaluated by the Clinical Dementia Rating scale sum-of-boxes (CDR-SB; $p=0.023$ vs. placebo; from MMRM analysis) and on motor function, as assessed by the Timed Up and Go Test (TUG; $p=0.044$ vs. placebo, from MMRM analysis). In secondary analyses, a dose of 40mg TID demonstrated significant (improvement compared to placebo on the primary endpoint (NTB composite, $p=0.049$), the Attention Composite ($p=0.023$), CDR-SB ($p=0.007$) and the TUG test ($p=0.024$). Neflamapimod was well tolerated in the study, with no early terminations or SAEs in patients receiving 40mg TID. Details of the clinical trial results are provided in the Investigator Brochure.

The primary objective of this study is to demonstrate the efficacy of neflamapimod, compared to placebo, as a treatment for DLB, as assessed by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB.

1.2. Pre-Clinical Pharmacology Results

There are no accepted preclinical models of DLB. However, the preclinical data obtained with neflamapimod to date provide evidence of its activity against specific pathophysiologic aspects of DLB regarded as the most important drivers of disease expression, specifically, synaptic dysfunction and forebrain cholinergic neuronal degeneration. To obtain preclinical proof-of-principle neflamapimod was tested for attenuation of age-dependent decline in hippocampal function in female Fischer rats (Alam, 2015). where the deficits in Morris water maze (MWM) performances have been argued to be due to deficient cholinergic input from the basal forebrain to the hippocampus (Dickinson-Anson, 2003). Neflamapimod, administered orally, twice per day (BID) for 3 weeks, fully reversed the spatial learning deficits in the MWM test in 20–22-month-old rats with identified cognitive deficits, demonstrating its ability to reverse the functional component of basal forebrain cholinergic dysfunction.

To address its ability to preserve cholinergic neurons, neflamapimod was tested in Ts2 mice, that model Down syndrome (DS) and develop a neurodegenerative pathology including basal forebrain cholinergic degeneration and endocytic abnormalities (Jiang et al, 2016). This pathology is particularly relevant to DLB, because, as noted above, it is considered to be a disease of forebrain cholinergic neuronal degeneration (Fujishiro et al, 2006). Ts2 mice were treated by oral gavage for 28 days, beginning at 4.7–6.4 months of age, when cholinergic neuronal loss is developing and endosomal pathology is evident, with either neflamapimod (3 mg/kg, BID) or vehicle. Wild-type mice were similarly treated for comparison. Neflamapimod treatment reversed the neurodegenerative phenotype, restoring cholinergic neuron counts in the medial septal nucleus (MSN) to levels comparable to those in wildtype mice with

neurons staining positive for choline acetyltransferase (ChAT) showing a more normal morphology (Jiang et al, 2022). Also reversed by neflamapimod treatment in Ts2 mice were endosomal abnormalities, as indicated by cortical counts of medium and large Rab5+ early endosomes ($P < 0.01$ vs vehicle). These findings demonstrate the potential of neflamapimod to be disease-modifying in a disease such as DLB that is driven by basal forebrain cholinergic neuronal loss.

1.3. Prior Clinical Experience

Neflamapimod has been tested clinically in AD, DLB, and also in earlier studies in rheumatoid arthritis and the risks to date are well documented.

Clinical safety data to support the use of neflamapimod 40 mg TID in the current clinical trial are available from four Phase 2 studies of ≥ 12 weeks treatment duration (see Table 1-1), one in patients with rheumatoid arthritis, and three in relevant disease indications, AD and DLB.

Table 1-1: Neflamapimod Phase 2 Clinical Studies ≥ 12 weeks Treatment Duration

Study #	Patient Population	Doses/ regimen used (mg)	24-hour plasma drug exposure
VX00-745-102	Rheumatoid Arthritis	Placebo (n=15), 250 b.i.d. (n=44) for 12 weeks	0.9 µg*hr/mL
VX00-745-302	Mild Alzheimer's Disease	Dose1: 40 mg b.i.d. (n=9) Dose2: 125 mg b.i.d. (n=7)	0.14 – 0.22 µg*hr/mL
EIP-VX17-745-304	Mild Alzheimer's Disease	Placebo (n=83), 40 mg b.i.d. (n=78)	0.14 µg*hr/mL
EIP19-NFD-501	Mild-to-Moderate Dementia with Lewy Bodies (DLB)	Placebo (n=45), 40 mg b.i.d. (n=26), 40 mg t.i.d. (n=20), weight based	0.14 – 0.18 µg*hr/mL

Due to the 95% protein binding in plasma, which reduces potency three-fold, the Phase 2 clinical study in rheumatoid arthritis (RA) was conducted at a significantly higher dose level than the studies in CNS indications, which resulted in a 24-hour plasma drug exposure 4.5-fold higher than the plasma drug exposure achieved with 40 mg TID. The dose limiting in this study was elevation in transaminase (ALT/AST) levels, which was seen in 6 of 44 (14% of patients); with Grade 1 elevation in 3 subjects, and Grade 2 elevation in 3 subjects. These elevations generally started at or around week 4 of treatment, reversed upon treatment cessation, and were not associated with bilirubin elevations. The most common treatment emergent adverse events (TEAEs) in the study in neflamapimod recipients in the RA study were abdominal pain (21% incidence vs. 0% in placebo) and diarrhea (18% vs. 0%), which generally were reported as being related to study drug.

The incidence TEAEs, regardless of relationship, for the three $\geq$ 12-week duration Phase 2 studies in AD or DLB is shown in Table 1-2. Notably, the incidence of gastrointestinal events is lower than reported in the study in RA, with a lower incidence of diarrhea and only one instance of abdominal pain in the trials in AD and DLB (not shown in table). With regard to relationship, in the case of the three most common events, 1 of 19 falls was considered related (possibly related in a placebo-recipient), 8 of the 17 diarrhea events were considered related (all possibly related, four in neflamapimod recipients) and 10 of the 15 headache events were considered related (all possibly related, eight in neflamapimod recipients).

Across the three studies, there has been one instance of treatment discontinuation in a neflamapimod recipient for a study drug related TEAE, which was a subject in the 24-week treatment study in AD who discontinued at the end of week 1 for a possibly-related event of mild nausea. There has been no study drug related serious adverse events reported from these clinical trials.

Table 1-2: Incidence of Treatment-Emergent Adverse Events (TEAEs) reported at >2% incidence in ≥ 12-week treatment duration studies in AD or DLB

	Placebo (N=128)	Neflamapimod (N=140)	Combined (N=268)
Falls	8 (6%)	11 (8%)	19 (7%)
Diarrhea	7 (6%)	10 (7%)	17 (6%)
Headache	6 (5%)	9 (6%)	15 (6%)
Common Cold/URI	8 (6%)	7 (5%)	15 (6%)
Nausea	4 (3%)	6 (4%)	10 (4%)
Somnolence	3 (2%)	4 (3%)	7 (3%)
Vomiting	4 (4%)	2 (1%)	6 (2%)
Fatigue	5 (3%)	1 (1%)	6 (2%)

With regard to laboratory abnormalities, there has been one instance of a Grade 1 elevation in ALT/AST elevations across the three Phase 2 clinical trials. The elevation was noted in a routine, per study protocol laboratory test evaluation at Week 8 and was associated with subject-reported moderate (14 units per week) alcohol intake. Of note, the subject, who was receiving neflamapimod 40 mg BID in the 24-week AD study, continued to take study drug for one week after the first lab test was taken, and a repeat evaluation showed a 50% reduction in ALT/AST levels during continued neflamapimod intake. At that time, study drug was discontinued, and the subject withdrew from the study, and no further follow-up information is available.

2. OBJECTIVES

2.1. Primary Objective

The primary objective is to demonstrate the efficacy of neflamapimod, compared to placebo, as a treatment for DLB, as assessed by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB).

2.2. Secondary Objectives

The secondary objectives are to:

- Demonstrate that neflamapimod improves motor function, compared to placebo, as assessed by the Timed Up and Go Test (TUG).
- Demonstrate that neflamapimod improves cognition, compared to placebo, as assessed by a DLB-specific Neuropsychological Test Battery (NTB). The NTB is comprised of:
    - Cogstate Detection test (DET)
    - Cogstate Identification test (IDN)
    - Cogstate One Card Learning test (OCL)
    - Cogstate One Back test (ONB)
    - Letter Fluency Test
- Demonstrate that neflamapimod improves global (cognition, function and behavior) disease status as evaluated by a clinician with caregiver input, compared to placebo, as assessed by the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC).

2.3. Exploratory Objectives

The exploratory objectives include:

- Change in Dementia Cognitive Fluctuations Scale (DCFS).
- Select domains of the 12-item Neuropsychiatric Inventory (NPI-12), including depression (dysphoria), apathy, hallucinations, and agitation/aggression.
- Change in hallucinations frequency x severity score within the NPI-12 in subjects who report hallucinations at baseline.
- Change in sleep and night-time behavior change within the NPI-12.
- Change in MDS-UPDRS3 motor examination (Part III) score.
- Change in beta functional connectivity and in alpha reactivity on quantitative EEG.
- Basal forebrain atrophy by structural MRI

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2b, multi-center, randomized, double-blind, placebo-controlled study of neflamapimod versus matching placebo (randomized 1:1) administered with food for 16 weeks in subjects with DLB. Subjects will receive 3 capsules per day (TID) with food (i.e., with the morning, mid-day, and evening meals), either neflamapimod 40 mg or placebo. Doses should be administered at least 3 hours apart.

3.1.1. Subject Recruitment

Subjects may be recruited to participate in this study via a number of methods based on each site's preference. Typical recruitment methods include advertising locally or on website/social media, referrals from other physicians, and the site's existing patient pool.

3.1.2. Screening

Following completion of informed consent procedures, subjects will enter the Screening phase of the study.

One to two Screening visits are planned, during which safety screening measures will be undertaken as well as some cognitive assessments (per Schedule of Assessments). A plasma sample for pTau181 analysis will also be obtained at Screening and analyzed for eligibility purposes. Screening will be conducted within 21 days before Baseline (Day 1). If a DaTscan™ is required to determine study eligibility, Screening may be extended to 35 days.

3.1.3. Treatment Period

Once eligibility is confirmed during the Screening period and before the first dose of study drug, subjects will be stratified by background dementia therapy (one of three strata: no cholinesterase inhibitor therapy, cholinesterase inhibitor therapy alone, or cholinesterase inhibitor therapy plus memantine therapy) and then be randomly assigned on a 1:1 basis to placebo or neflamapimod for the 16-week treatment period. Investigators and subjects will be blinded to the treatment assignment.

Dosing will start on Day 1 following completion of all baseline procedures. During the 16-week treatment period, subjects will return to the clinic every 2 weeks for the first month and then every 4 weeks thereafter. A Final Study Visit (i.e., Follow-Up Visit) will be conducted 2 weeks (±3 days) after completion of study drug or after the Early Termination (ET) visit. See the Schedule of Assessments for details regarding when assessments are conducted.

3.1.4. Early Termination (ET)

Subjects who prematurely discontinue study drug for any reason will be asked to return to the clinic for an Early Termination (ET) visit within 3 days following the last study drug dose; if it is determined that the subject will discontinue study drug while at the study center for a scheduled visit, then the ET visit should be conducted at that time. These subjects will also be asked to return to the clinic for a Follow-up Visit 2 weeks (±3 days) following the last study drug dose. If possible, the subject will also be asked to return to the clinic at Week 16 for their end of study visit if the Follow-up visit is prior to Week 12.

Every effort should be made to ensure a subject returns for these visits.

Refer to Section 4.3 for details regarding removal of subjects from treatment.

3.1.5. Extension Treatment

All subjects who complete the 16-week treatment phase will be offered the opportunity to continue in an open-label extension treatment where they will be provided neflamapimod TID for an additional 32 weeks. Patients who enter the extension phase will remain blinded to their previous treatment until the database has been locked and results are compiled in the parent study. Based on the results of the double-blind treatment phase of the study, EIP Pharma will work with each country to provide access to treatment after completion of the extension phase, if there is a clear benefit.

3.2. Discussion of Study Design

The study is being conducted to confirm the clinical findings in the exploratory (hypothesis-generating) Phase 2a clinical study of neflamapimod in Dementia with Lewy bodies in a larger hypothesis-testing Phase 2b clinical study. As such, the study design is similar to the Phase 2a study (e.g., 16-week treatment duration), but with refinements based on learnings obtained in phase 2a. Specifically, the primary outcome measure for the current study will be the CDR-SB, an endpoint that demonstrated higher sensitivity for treatment effects in the phase 2a study than the neuropsychological test battery assessing attention, executive function and visuospatial function), which was the primary outcome measure in phase 2a. The better performance of CDR-SB, relative to that of the Neuropsychological Test Battery (NTB), is potentially due to a number of factors, including (1) the ability of the CDR-SB to capture effects on both cognitive and motor function, (2) the CDR-SB being primarily based on caregiver input, which may be less prone than cognitive testing of the patient to external factors (e.g., pandemic) and day-to-day fluctuation, and (3) through the functional domains, as well the open ended questions within the cognitive domains, the ability to capture cognitive domains that are not assessed by the tests within the NTB (which by design are meant to capture effects on specific cognitive domains).

The inclusion/exclusion criteria are largely the same as in phase 2a. Two additions to the inclusion/exclusion criteria are designed to reduce heterogeneity within the population randomized. First, only patients with global CDR scores (CDR-GS) of 0.5 and 1.0 will be enrolled. In Phase 2a, participants with CDR-GS 2.0 were also enrolled, though only 7 of the 91 participants randomized had a baseline CDR-GS of 2.0. Within that small number, there was an impression that the treatment response was minimal in the participants with baseline CDR-GS of 2.0. The more important refinement of the population to be enrolled is that patients with baseline plasma ptau181 greater than a threshold associated with Alzheimer's disease (AD) co-pathology will be excluded. Elevated plasma ptau181 predicts the presence of temporal lobe tau pathology (Hall et al, 2021) and is associated with more advanced disease and more rapid cognitive decline (Gonzales et al, 2022). In the Phase 2a study, elevated plasma ptau181 was associated with lower effect size for neflamapimod vs. placebo, while the effect size for neflamapimod vs. placebo in patients without elevated plasma ptau181 was 0.74 for each of CDR-SB and TUG, and 0.56 for the NTB (cognitive test battery).

The combined effect of not enrolling patients with CDR-GS of 2.0 and excluding patients with elevated plasma ptau181 will be to enroll patients at a less advanced stage of disease than in phase 2a, patients who may be more likely not to be receiving cholinesterase inhibitor therapy. As such, as opposed to phase 2a where all patients were receiving cholinesterase inhibitor therapy, patients who are not receiving cholinesterase inhibitor therapy will not be excluded in the current study.

With respect to the EEG, beta functional connectivity is the primary outcome measure, and Eyes Closed (EC)-to-Eyes Open (EO) alpha reactivity is the one secondary EEG endpoint. Beta functional connectivity is the primary EEG endpoint because there was a signal for a treatment effect in the Phase 2a study. EEG assessments were included in our Phase 2a study but unfortunately could not be obtained in all patients at the planned 16-week timepoint because of COVID-19-related restrictions; nonetheless, significant (after correction for multiplicity) dose-dependent improvement in beta-functional connectivity was observed, with no other evident effects that survived adjustment for multiple testing. We hope to confirm this finding in the proposed Phase 2b study. EC-to-EO alpha reactivity was not evaluated in the Phase 2a study, but is included as secondary EEG endpoint because a new report (Schumacher et al. 2020; Jennings et al, 2022, published after the Phase 2a study was conducted) indicates that alpha reactivity is a specific measure for DLB and a measure of "cholinergic integrity" in both DLB and AD.

The current study will also include structural and functional MRI to evaluate the effects on atrophy of the basal forebrain cholinergic system, as well the integrity of the functional connectivity pathways of the basal forebrain. Cholinergic neuronal degeneration in the basal forebrain is prominent in DLB and neflamapimod has demonstrated potential to impact the degenerative process in the basal forebrain (Jiang et al, 2022). The inclusion of MRI studies is the major difference between this, the ex-US version, and the protocol within the US.

The final change from Phase 2a is that all participants in the current study will receive 40mg TID if randomized to neflamapimod, while in Phase 2a those with weight < 80kg received 40mg BID. See the next section for further discussion for the selection of 40mg TID for the current study.

3.2.1. Rationale for Dose Selection

3.2.1.1. Efficacy Considerations

40 mg neflamapimod capsules three times daily (TID), taken with food, is the dose and regimen that will be utilized in this study. This dose and regimen demonstrated clinical efficacy in the aforementioned Phase 2a clinical study in DLB (EIP19-NFD-501, Study 501; see Section 1.1). The other dose regimen utilized in the study, 40 mg neflamapimod BID, demonstrated heterogenous effects on the major endpoints in the Study 501, including little to no effect on the primary outcome measure, the NTB. The magnitude of the efficacy in Study 501, particularly with respect to the CDR-SB, is such that a higher dose is considered not necessary to evaluate.

The dose response seen in 501 is consistent with a threshold effect of trough plasma drug concentrations on efficacy, derived from the clinical trials in Alzheimer's disease (AD). The clinical endpoint in the AD trials that is most comparable to the NTB utilized in the Phase 2 DLB study (Study 501) is the Wechsler Memory Scale (WMS) Immediate and Delayed Recall. The WMS Immediate/Delayed Recall also consists of six cognitive tests, and while its primary focus is to measure effects on episodic memory it is also dependent on attention, executive function and visuospatial functions (as is the case with the DLB-specific NTB). In the 24-week placebo-controlled study in early AD ("REVERSE-SD" study; Prins et al, 2021), an effect on WMS Immediate/Delayed Recall with 40 mg BID was only seen in patients on background therapy who achieved plasma drug levels > 4 ng/mL, levels that would be expected with 40 mg TID, but not with 40mg BID. In addition, there were positive trends towards less worsening compared to placebo on the CDR-SB in the REVERSE-SD study (Prins et al, 2021). In the six-week study in Phase 2a, a similar plasma drug concentration dependent threshold effect on a biomarker, cerebrospinal fluid IL-8 levels, was also demonstrated.

3.2.1.2. Safety Considerations

Based on the clinical experience to date at higher doses, the TID results in the 501 study as well as the PK results noted above, neflamapimod dose of 40 mg TID is well tolerated and has a low risk of drug toxicity.

The expected the estimated average AUC24 that will result with the 40 mg TID dose regimen to be utilized in the study is approximately 0.2 µg*hr/mL. This exposure will provide greater than a 10-fold margin to the no-effect exposure level in the chronic repeat dose studies in rat and the dog (see Investigator Brochure). From a clinical safety standpoint, the dosing regimen and exposure level are supported by safety data obtained from approximately 300 healthy volunteers and patients who have received neflamapimod for up to six months. The highest plasma drug exposure levels obtained in patient-based clinical studies was in rheumatoid arthritis (RA), where 750 mg BID for 28 days (N=6) resulted in AUC24 steady-state of ~ 1.5 µg*hr/mL and 250 mg BID for up to 12 weeks (N=44) resulting in AUC24 at steady-steady state 0.9 µg*hr/mL. The dose-limiting adverse effect across these studies were reversible transaminase elevation, most evident at 250 mg BID for 12 weeks in patients with RA where 6 of 44 patients developed ≥ Grade 1 elevation in ALT and/or AST. In the relevant patient populations of AD and DLB, to date, Grade 1 elevation of ALT/AST was seen in one of 126 patients (the one elevation developed at week 12) who received 40 mg BID for up to 24 weeks, 0 of 8 patients who received 125 mg BID for 12 weeks, and 0 of 20 patients who received 40 mg TID for 16 weeks. This study will include a monitoring plan for ALT/AST elevation and specific criteria for dose interruption and dose discontinuation for abnormalities in these parameters. A broader summary of the clinical safety experience to date will be provided in the Investigator Brochure.

In the recently completed DLB 501 Study, neflamapimod was well tolerated. No new safety signals were identified in this study. There were ten (10) early treatment discontinuations, 4 due to adverse events and/or disease worsening (1 in placebo BID and 3 in neflamapimod BID recipients), 4 due to withdrawal of consent (1 in placebo BID and 3 in neflamapimod BID), 1 due to death (in placebo BID), and 1 due to physician decision (in placebo TID). There were 4 serious adverse events (SAEs) reported in the placebo group (hematochezia, intraparenchymal hemorrhage, internal bleeding and asthma exacerbation) and 3 in neflamapimod BID recipients (new brain lesions, brain tumor, head injury), all of which were considered unrelated to study drug administration. There were no SAEs or early treatment discontinuations amongst 40 mg neflamapimod TID recipients, the dose level in the current protocol. One patient decreased dose from TID to BID due to worsening of orthostatic hypotension.

Treatment-emergent adverse events (TEAEs), regardless of relationship, reported in greater than one neflamapimod subjects are as follows (incidence in neflamapimod; placebo): Falls (13%;9%), Headache (9%;4%), Diarrhea (7%;11%), Nausea (7%;7%), Common cold (4%;2%), Head injury (4%;0%), Light headedness (4%;2%), Memory Impairment (4%;0%).

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4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects meeting all of the following criteria are eligible for enrollment in this study:

1. Men and women aged ≥55 years.
2. Subject is willing and able to provide written informed consent.
3. Probable DLB by consensus criteria (McKeith et al, 2017), including a positive DaTscan™. If the DaTscan is negative, but the subject has historical polysomnography (PSG)-verified REM sleep behavioral disorder (RBD), this will also qualify as probable DLB.
4. CDR Global Score of less than 2.0 at Screening.
5. If the patient is currently receiving cholinesterase inhibitor therapy, the patient must have received such therapy for greater than 3 months and on a stable dose for at least 6 weeks at the time of randomization. Except for reducing the dose for tolerability reasons, the dose of cholinesterase inhibitor may not be modified during the study. If the patient is not currently receiving cholinesterase inhibitor therapy, but received such therapy previously, that therapy must have been discontinued at least 3 months prior to randomization. Memantine therapy is allowed, if it had been started at least 3 months prior to randomization and the patients is also receiving cholinesterase inhibitor therapy (memantine monotherapy, i.e., without concomitant cholinesterase inhibitor therapy, is excluded).
6. Normal or corrected eyesight and auditory abilities, sufficient to perform all aspects of the cognitive and functional assessments.
7. No history of learning difficulties that may interfere with their ability to complete the cognitive tests.
8. Received vaccination for SARS-CoV-19, unless medical contraindications prevent being vaccinated, or has a history of natural infection.
9. Must have reliable informant or caregiver.

4.2. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for enrollment in this study:

1. Diagnosis of any other ongoing CNS condition other than DLB, including, but not limited to, post-stroke dementia, vascular dementia, AD, or PD.
2. Plasma ptau181 result above the threshold that indicates evidence of pathology associated with Alzheimer's disease) at Screening.
3. Suicidality, defined as active suicidal thoughts within 6 months before Screening or at Baseline, defined as answering yes to items 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS), or history of suicide attempt in previous 2 years, or, in the Investigator's opinion, at serious risk of suicide.

4. Ongoing major and active psychiatric disorder and/or other concurrent medical condition that, in the opinion of the Investigator, might compromise safety and/or compliance with study requirements.
5. Diagnosis of alcohol or drug abuse within the previous 2 years.
6. Poorly controlled clinically significant medical illness, such as hypertension (blood pressure >180 mmHg systolic or 100 mmHg diastolic); myocardial infarction within 6 months; uncompensated congestive heart failure or other significant cardiovascular, pulmonary, renal, liver, infectious disease, immune disorder, or metabolic/endocrine disorders or other disease that would interfere with assessment of drug safety.
7. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio (INR) >1.5.
8. Known human immunodeficiency virus, hepatitis B, or active hepatitis C virus infection.
9. Participated in a study of an investigational drug less than 6 weeks or 5 half-lives of an investigational drug, whichever is longer, before enrollment in this study.
10. History of previous neurosurgery to the brain within the past five years.
11. If male with female partner(s) of child-bearing potential, unwilling or unable to adhere to contraception requirements specified in the protocol.
12. If female who has not has not reached menopause >1 year previously or has not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy, has a positive pregnancy test result during Screening and/or is unwilling or unable to adhere to the contraception requirements specified in the protocol.

4.3. Removal of Subjects from Treatment

In accordance with the current revision of the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. A subject's participation may also be discontinued by the Investigator or Sponsor due to compliance, safety, or other administrative reason (see also Section 6.2.11).

The subject **must** be discontinued from study drug treatment for the occurrence of an unacceptable toxicity, including any of the following:

- Any clinically significant infection. (Clinically significant is defined as any infection requiring hospitalization and/or intravenous antibiotics and/or considered to be opportunistic.)
- Elevated ALT or AST, including:
    - ALT or AST >8×ULN
    - ALT or AST >5×ULN for >2 weeks
    - ALT or AST >3×ULN and total bilirubin >2×ULN or INR >1.5xULN
    - ALT or AST >3×ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

Refer to Section 3.1.3 for details regarding follow-up after early discontinuation. Additional care and treatment will be provided to subjects once study discontinuation, including any required follow-up visits for resolution for study-related AEs, is completed.

5. TREATMENTS ADMINISTERED

All subjects will be administered 1 capsule of neflamapimod 40 mg capsules or matching placebo, orally TID with food (i.e., with the morning, mid-day, and evening meals) for 16 weeks. The initial treatment phase of the study will be blinded. Patients who complete the parent study may be eligible for a further 32 weeks of treatment (neflamapimod 40mg TID) in an open-label extension.

Doses must be taken within 30 minutes following a meal or snack. Doses should be taken at approximately same times each day throughout the study and at least 3 hours apart.

5.1. Dosing

The first dose of study drug (on Baseline/Day 1) will be administered at the study center. The Investigator or other designated, qualified site personnel should review dosing instructions with the subject prior to the subject leaving the site. Subjects will be instructed to return all study containers, regardless of whether empty or containing unused study drug.

If the subject's Day 1 visit is in the afternoon, the subject should only administer 2 doses (instead of 3) on Day 1.

If a subject misses 1 study drug dose (i.e., 1 capsule), the subject should resume dosing at the next scheduled administration time, at which time both the missed dose and the current dose (i.e., 2 capsules) are to be taken. If the subject misses 2 study drug doses (i.e., 2 capsules), the subject should take 2 doses (i.e., 2 capsules) at the next scheduled administration time, and then resume regular dosing (i.e., 1 capsule) at the next scheduled administration time. Subjects should not take more than 2 doses (i.e., 2 capsules) at any given administration time.

5.2. Dose Modifications, Interruptions or Discontinuation

For tolerability reasons after at least two weeks of treatment, the Investigator may request and receive approval from the Medical Monitor to modify from 40 mg TID to 40 mg BID in subjects with weight less than 70 kg. No other dose modifications are permitted during the study. If a subject is unable to tolerate the assigned study drug dose then the subject should be discontinued from study drug treatment (Section 4.3).

5.3. Packaging and Labeling

EIP Pharma will supply placebo or neflamapimod capsules via blister packs on an individual subject basis. Both neflamapimod and placebo capsules are red in color.

Label details will be in accordance with local and national requirements.

5.4. Study Drug Supply, Storage, and Handling

Study drug will be supplied to sites on an individual subject basis. Neflamapimod capsules should be stored at room temperature.

While at the clinical site, study drug access should be limited to the Investigator and other qualified site personnel.

5.5. Drug Accountability, Disposal, Return, or Retention Study Drug

The site designated pharmacist or other qualified personnel will document receipt from Sponsor, dispensing to subjects, and return to the study center from subject via drug accountability log(s).

Subjects will be instructed to return all blister packs to the study center, regardless of whether empty or containing unused study drug. EIP Pharma or designee will review accountability records throughout the conduct of the study.

The site should maintain all study drug containers (used and unused) until final review of accountability is conducted by the EIP Pharma or designee, and instructions regarding return or disposal, as applicable, are provided.

5.6. Treatment Compliance

Treatment compliance will be assessed by reviewing the count of returned capsules at each visit. Any apparent discrepancies between quantity of capsules returned and the number expected based on dosing schedule will be discussed with the subject to ensure an understanding of dosing instructions.

Compliance is defined as $\geq$80% at each visit. If compliance is <80%, this is a protocol deviation. Repeated non-compliance with dosing instructions may necessitate discontinuation from the study, based on the Investigator's judgment (Section 4.3).

5.7. Method of Assigning Subjects to Treatment Group

Once eligibility is confirmed, subjects will be stratified by background dementia therapy (one of three strata: no cholinesterase inhibitor therapy, cholinesterase inhibitor therapy alone, or cholinesterase inhibitor therapy plus memantine), and then randomized on a 1:1 basis in a blinded manner to receive either placebo or 40 mg neflamapimod utilizing an automatically generated random code. Randomization will be administered via Interactive Response Technology (IRT).

5.8. Study Blinding and Breaking the Blind

Subjects and site personnel associated with study conduct will be blinded to treatment assignment.

During the conduct of the study, the blind should be broken on an individual subject basis in the event of an emergency where it is necessary for the Investigator to know which treatment the subject is receiving before the subject can be treated. The blind may also be broken if someone not in the study uses study drug (e.g., if a child in the participant's household takes study drug, the blind may be broken to determine treatment for the child).

When it is necessary to break the blind, the Investigator may unblind the treatment immediately (i.e., without prior notice to the Medical Monitor, Sponsor, or other) but must notify the Independent Ethics Committee (IEC) per local regulations and Sponsor as soon as possible, preferably by telephone and then in writing, regarding the necessity of code breaking.

If the code is broken for a subject, this must be documented in the electronic case report form (eCRF) and source documents, together with the reasons for breaking the code.

5.9. Prior and Concomitant Therapy

Any medications taken from Screening through the Final Study Visit (i.e., Follow-Up Visit), including all prescription and over-the-counter medications as well as supplements, will be documented in the subject's source document and in the eCRF.

While drug-drug interaction studies have not been conducted, in vitro testing indicates that neflamapimod is metabolized by oxidation in the liver by the cytochrome P450 (CYP) system (combination of CYP3A4 and CYP2C19 isozymes). Until the metabolism is better characterized, **concomitant strong inhibitors of CYP3A4 are prohibited** and **strong inducers of CYP3A4 should be used with caution** in subjects receiving neflamapimod, as the use of such drugs could impact neflamapimod metabolism in subjects who have an underlying CYP2C19 genotypic variant that impacts activity of that CYP2C19.

The following medications are prohibited during study participation:

- Strong CYP3A4 inhibitors (see Table 5-1).
- Any other investigational drug. If a subject has previously participated in a study of an investigational drug, last dosing must have occurred 3 months or 5 half-lives of the investigation drug, whichever is longer, before enrollment in this study.

The Medical Monitor should be contacted with any questions regarding concomitant use of medications that are thought to modulate CYP3A4 activity.

Table 5-1: CYP3A4 Inhibitors

Prohibited: **Strong Inhibitors** **≥5-fold increase in AUC** **or >80% decrease in CL**	**Allowed:** **Moderate inhibitors** **≥2 but <5-fold increase in AUC** **or 50-80% decrease in CL**	**Allowed:** **Weak inhibitors** **≥1.25 but <2-fold increase in AUC** **or 20-50% decrease in CL**
boceprevir cobicistat clarithromycin conivaptan danoprevir/ritonavir diltiazem elvitegravir/ritonavir grapefruit juice idelalisib indinavir/ritonavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir paritaprevir/ritonavir/ombitasvir posaconazole ritonavir saquinavir/ritonavir telaprevir tipranavir/ritonavir troleandomycin voriconazole	Aprepitant cimetidine ciprofloxacin clotrimazole crizotinib cyclosporine dronedarone erythromycin fluconazole fluvoxamine imatinib tofisopam verapamil	chlorzoxazone cilostazol fosaprepitant istradefylline ivacaftor lomitapide ranitidine ranolazine tacrolimus ticagrelor

Abbreviations: AUC, area under the concentration-time curve; CL, clearance.

Table 5-2: CYP3A4 Inducers

Use with Caution: Strong Inducers ≥80% decrease in AUC	Allowed: Moderate Inducers 50-80% decrease in AUC	Allowed: Weak Inducers 20-50% decrease in AUC
carbamazepine enzalutamide mitotane phenytoin rifampin St. John's wort	bosentan efavirenz etravirine modafinil	armodafinil rufinamide

Abbreviations: AUC, area under the concentration-time curve.

5.10. Contraception and Pregnancy

This section should be read in conjunction with the selection criteria that relate to age and contraception:

- Exclusion criteria #11 and #12 (Section 4.2)

No signs of embryo-fetal toxicity or teratogenic effects of neflamapimod were observed in rats. Testing in rabbits was not performed due to lack of exposure following administration of the neflamapimod formulation. No human studies of effects of neflamapimod on conception, pregnancy, or lactation have been performed. Females should not be exposed to neflamapimod if pregnant, breastfeeding, or attempting to conceive. The following guidelines for contraception should be followed from before first dose on Day 1 through 91 days following the last dose of study drug.

5.10.1. Female Contraception

Female subjects of child-bearing potential (have not experienced menopause and have not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy) or female subjects who have experienced menopause within the previous year must have a negative pregnancy test during Screening and must use at least 1 of the following contraceptive methods:

- Complete abstinence regardless of menstrual cycle timing
- Contraceptive (oral, transdermal, injectable, or implantable), intrauterine device, or barrier method of contraception

5.10.2. Male Contraception

Male subjects with female partners of child-bearing potential must use at least 1 of the following contraceptive methods:

- Hormonal contraceptives (oral, injectable, patch, intrauterine devices)
- Male sterilization
- Total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the subject

- Abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments when this is the preferred and usual lifestyle of the subject
- Note that periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception

5.10.3. Pregnancy

Any pregnancy should be reported to the Investigator, and, in turn, the pregnancy should be reported to the Sponsor or designee within 24 hours of the Investigator's awareness of the pregnancy. If a female subject becomes pregnant, study drug will be permanently discontinued and the subject will be discontinued from the study.

With proper informed consent (separate pregnancy informed consent form), the subject or partner will be followed through the completion of the pregnancy and outcome of the pregnancy reported, and the infant will be followed for 12 months after birth.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Schedule of Assessments

Table 6-1: Schedule of Assessments (Treatment Phase)

	Screening	Treatment Phase						Early Termination	Follow-Up
	Screening Visit[a]	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	ET Visit[c]	Follow-Up Visit[d]
Assessment	Within 21 days of D1[a]	D1[b]	D14 (±3)	D28 (±5)	D56 (±5)	D84 (±5)	D112 (±5)	Within 3 days after last dose	Within 14 days (±3) of last dose
Informed Consent	X[e]						X[e]		
Medical history review	X								
MMSE	X								
Physical examination[f]	X						X	X	X
Vital signs[g]	X	X	X	X	X	X	X	X	X
Pregnancy testing	X[h]								
Hematology and chemistry[i]	X	X		X	X	X	X	X	
Coagulation studies[i]	X						X	X	
12-lead electrocardiogram[j]	X								
DaTscan™, if needed	X[k]								
MRI	X[l]	X[m]					X[m]		
C-SSRS	X	X		X	X	X	X	X	
CDR-SB	X	X		X	X	X	X	X	
NTB[n]	X	X		X	X	X	X	X	
TUG	X	X			X	X	X	X	
ADCS-CGIC		X					X	X	
DCFS	X	X		X	X	X	X	X	
NPI-12		X				X	X	X	
MDS-UPDRS3 (Part III)		X			X		X	X	
EEG[o]		X					X[p]	X	
Dispense study drug		X	X	X	X	X	X[q]		

	Screening	Treatment Phase						Early Termination	Follow-Up
	Screening Visit[a]	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	ET Visit[c]	Follow-Up Visit[d]
Assessment	Within 21 days of D1[a]	D1[b]	D14 (±3)	D28 (±5)	D56 (±5)	D84 (±5)	D112 (±5)	Within 3 days after last dose	Within 14 days (±3) of last dose
Pharmacokinetic (PK) sampling			X[r]						
Plasma sample for pTau181	X[s]								
Plasma sample for protein biomarker testing	X	X				X	X	X	
Prior/concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event recording	X	X	X	X	X	X	X	X	X
Final study drug reconciliation							X	X	

ADCS-CGIC: Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes
CT: Computed tomography
D: day
DCFS: Dementia Cognitive Fluctuations Scale
MDS-UPDRS3: Movement Disorder Society – Unified Parkinson's Disease Rating Scale – Part III
MMSE: Mini mental state exam
MRI: Magnetic resonance imaging
NPI-12: 12-item Neuropsychiatric Inventory
NTB: Neuropsychological Test Battery

a. One to two Screening visits are planned during which safety screening procedures are to be completed and reviewed, including at least two (2) practice NTB evaluations and the required diagnostic and cognitive impairment procedures. Screening will be conducted within 21 days before Baseline (Day 1); if a DaTscan and/or MRI is required to determine study eligibility, Screening may be extended to 35 days. (If necessary, a second visit may be conducted on a different day to allow for scheduling purposes.)
b. On Day 1, all procedures should be conducted prior to first dose of study drug.
c. Subjects who prematurely discontinue study drug for any reason will be asked to return to the study center for an Early Termination (ET) visit within 3 days following the last study drug dose; if it is determined that the subject will discontinue study drug while at the study center for a scheduled visit, then the ET visit should be conducted at that time.

d. The Follow-up Visit should be conducted within 14 (±3) days of the last dose of study drug for subjects who complete the main study or discontinue early. **If subjects are continuing in the Extension Phase, the Follow-Up Visit does not need to be conducted following their completion in the Treatment Phase since they will be continuing on study drug.**

e. Informed consent procedures, including signing of informed consent, must be completed before any study-specific procedures are performed. If subject is continuing to Extension Phase, consent should be completed at the Week 16 visit of the Treatment Phase prior to any study-specific procedures for the Extension Phase are performed.

f. Refer to Section 6.2.5 for details regarding physical examination.

g. Vital signs include blood pressure, pulse, respiratory rate, and body temperature. Vital signs should be measured after the subject has been in sitting position for 5 minutes.

h. Female subjects of child-bearing potential or who have reached menopause in the previous year must have a serum or urine pregnancy test performed during Screening; subjects with positive results are not eligible for study participation.

i. Details of clinical laboratory sampling for chemistry, hematology, and coagulation studies are discussed in Section 6.2.8

j. Details of 12-lead ECG assessment are discussed in Section 6.2.7.

k. Subjects are required to have a prior DaTscan. If a DaTscan has not been performed within the previous 2 years, it is to be performed during Screening **only after** subject has been deemed eligible based on all other inclusion/exclusion criteria (e.g., medical history, laboratory testing) and prior to randomization. Note that if DaTscan results are negative (i.e., no evidence of reduced uptake in the basal ganglia), the subject is required to have historical PSG-verified RBD to be eligible for study participation.

l. If MRI or CT has not been performed within 3 years before Screening and/or results are not available, a MRI must be performed to exclude other disease as part of Screening **only after** subject has been deemed eligible based on all other inclusion/exclusion criteria (e.g., medical history, laboratory testing) and prior to randomization (see Section 6.2.2). This MRI will also be considered the subject's Baseline MRI.

m. For sites outside the US, a MRI will be performed at Baseline (pre-dose) if one was not done at Screening. A MRI will also be performed at Week 16 in the Treatment Phase and Week 32 in the Extension Phase.

n. Refer to Section 6.2.4.2 for details regarding the NTB, which will include all tests in the secondary endpoint, as well the Category Fluency Test (CFT) and the International Shopping List Test (ISLT).

o. In the Treatment Phase, an EEG does not need to be performed at the ET visit for subjects who discontinue prior to Week 4 (Day 28). Refer to Section 6.2.6 for further details regarding EEG assessments.

p. The EEG at Week 16 can be completed anytime between Weeks 12 and 16. EEG will not be conducted at sites that do not have access to an EEG facility.

q. **If subject is continuing in open-label extension treatment, open-label neflamapimod study drug should be dispensed at Week 16 visit. This visit will also be the Day 1 visit of the extension treatment.**

r. At the Week 2 visit in the Treatment Phase, one (1) PK plasma samples will be obtained ***pre-dose***. Subjects will be instructed to not take their first dose on the mornings of the Week 2 visit; and instead take their dose with a snack at the site after the pre-dose PK sample is obtained. Refer to Section 6.2.9 for further details regarding PK sampling.

s. A plasma sample for pTau181 analysis will be obtained at Screening and evaluated for eligibility purposes. Refer to Section 6.2.10 for further details regarding pTau sampling and analysis.

Table 6-2: Schedule of Assessments (Extension Phase)

Assessment	Week 2*	Week 4	Week 8	Week 16	Week 32	ET Visit[c]	Follow-Up Visit[t]
	D14 (±3)	D28 (±5)	D56 (±5)	D112 (±5)	D168 (±5)	Within 3 days after last dose	Within 14 days (±3) of last dose
Physical examination[f]					X	X	X
Vital signs[g]		X	X	X	X	X	X
Hematology and chemistry[i]		X	X	X	X	X	
Coagulation studies[i]					X	X	
C-SSRS			X	X	X	X	
CDR-SB			X	X	X	X	
NTB[n]			X	X	X	X	
TUG			X	X	X	X	
ADCS-CGIC			X	X	X	X	
DCFS			X	X	X	X	
NPI-12			X	X	X	X	
MDS-UPDRS3 (Part III)			X	X	X	X	
MRI					X		
EEG[o]				X			
Dispense study drug		X	X	X			
Pharmacokinetic (PK) sampling		X[u]					
Plasma sample for protein biomarker testing			X		X	X	
Prior/concomitant medication	X	X	X	X	X	X	X
Adverse event recording	X	X	X	X	X	X	X
Final study drug reconciliation					X	X	

*Week 2 in the Extension Phase will be a telephone call to inquire about adverse events and any new concomitant medications. Following the telephone call, subjects may be seen in clinic at the Investigator's discretion.

c. Subjects who prematurely discontinue study drug for any reason will be asked to return to the study center for an Early Termination (ET) visit within 3 days following the last study drug dose; if it is determined that the subject will discontinue study drug while at the study center for a scheduled visit, then the ET visit should be conducted at that time.

f. Refer to Section 6.2.5 for details regarding physical examination.

g. Vital signs include blood pressure, pulse, respiratory rate, and body temperature. Vital signs should be measured after the subject has been in sitting position for 5 minutes.

i. Details of clinical laboratory sampling for chemistry, hematology, and coagulation studies are discussed in Section 6.2.8.

n. Refer to Section 6.2.4.2 for details regarding the NTB, which will include all tests in the secondary endpoint, as well the Category Fluency Test (CFT) and the International Shopping List Test (ISLT).

o. Refer to Section 6.2.6 for further details regarding EEG assessments. EEG will not be conducted at sites that do not have access to an EEG facility.

t. The Follow-Up Visit should be conducted within 14 (±3) days of the last dose of study drug for subjects who complete the Extension study or discontinue early.

u. At the Week 4 visit in the Extension Phase, one (1) PK plasma samples will be obtained ***pre-dose***. Subjects will be instructed to not take their first dose on the mornings of the Week 4 visit; and instead take their dose with a snack at the site after the pre-dose PK sample is obtained. Refer to Section 6.2.9 for further details regarding PK sampling.

6.2. Study Assessments

The subject must provide written informed consent before the performance of any study-related procedures.

The assessments below will be conducted at the time points specified in Table 6-1 and Table 6-2.

6.2.1. Baseline and Disease Characteristics

Details regarding DLB history, including method(s) of diagnosis will be collected during Screening, as specified in the eCRF. Subjects without documentation of prior diagnostic DLB tests (DaTscan and/or known amyloid biomarker status) are to have such tests performed during Screening (see Section 6.2.3).

6.2.2. Magnetic Resonance Imaging (MRI)

An MRI (structural and resting-state functional) will be performed as part of Baseline/Screening and at Week 16 of the Treatment Phase and Week 32 of the Extension Phase, to look at changes in atrophy of the basal forebrain, as well as its functional connectivity. The MRI at screening is to also to exclude other neurodegenerative or brain disease that could account for their cognitive symptoms.

If the subject is unable or unwilling to do an MRI at entry and Week 16, the subject must have had MRI or CT scan within 3 years of Screening, with findings negative for evidence of other neurodegenerative or other brain disease that could account for their cognitive symptoms. MRI/CT results should be available and reviewed before Screening diagnostic tests are performed.

6.2.3. DaTscan (if required)

Subjects are required to have a prior DaTscan (i.e., single-photon emission computed tomography [SPECT] with Ioflupane I 123 Injection) to be eligible for study participation.

The DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using SPECT brain imaging. Ioflupane I 123 Injection is to be administered and SPECT imaging is to be performed and interpreted per the prescribing information. If a DaTscan has not been performed within the previous 2 years, it is to be performed during Screening **only <u>after</u>** subject has been deemed eligible based on all other inclusion/exclusion criteria (e.g., medical history, laboratory testing) and prior to randomization.

NOTE: If DaTscan results are negative (i.e., no evidence of reduced uptake in the basal ganglia), the subject is required to have historical PSG-verified RBD to be eligible for study participation.

6.2.4. Clinical Outcome Evaluations

6.2.4.1. Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB)

The Clinical Dementia Rating Scale (CDR) (Hughes, 1982) is a semi-structured interview resulting in a semi-quantitative scoring of cognitive impairment in milder and more progressed forms of dementia. The CDR yields both a global score (CDR-GS) and Sum of Boxes score (CDR-SB). While the CDR-GS is typically utilized for staging purposes, the CDR-SB score is a more detailed quantitative general index than the CDR-GS (O'Bryant, et al, 2010), allowing the CDR-SB to be utilized as an outcome measure in clinical trials. Though there is limited experience with the CDR-SB in DLB, it has been utilized extensively in both longitudinal and treatment trials in both AD dementia and Mild Cognitive Impairment and is a regulatory endpoint for approval recognized by the FDA in those contexts.

The CDR interview is to be conducted with the subject and caregiver by an experienced and certified clinician.

6.2.4.2. Neuropsychological Test Battery (NTB)

The Neuropsychological Test Battery includes:

- Cogstate Detection test (DET): The DET is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli.
- Cogstate Identification test (IDN): The IDN is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli.
- Cogstate One Card Learning test (OCL): The OCL is a measure of visual learning and uses a well-validated pattern separation paradigm with playing card stimuli.
- Cogstate One Back test (ONB): The ONB is a measure of working memory and executive function that uses a well-validated n-back paradigm with playing card stimuli.
- Letter Fluency Test: The Letter Fluency Test is a measure of phonemic fluency. The test uses the 3-letter set of F, A, and S or C, F, and L to assess phonemic fluency. Individuals are given 1 minute to name as many words as possible beginning with one of the letters. The procedure is then repeated for the remaining two letters. The administration of phonemic and semantic fluency takes approximately 5 minutes. Admissible responses are summed and compared to a normative sample.

Additionally, the CFT and ISLT will be performed at the same time as the NTB:

- Category Fluency Test (CFT): The CFT is a measure of verbal fluency and is sometimes called semantic fluency. In the standard version of the task, participants are given 1 minute to produce as many unique words as possible within a category. The subject's score is the number of unique correct words.
- International Shopping List Test (ISLT): The ISLT is a measure of verbal learning and uses a well-validated list-learning paradigm. The subject is read a shopping list by the test supervisor and must remember and recall as many items from the list as possible.

The DET, IDN, OCL, ONB and ISLT are administered via a computer or Chromebook. The Letter Fluency Test and CFT are administered via paper scales. For purposes of the primary analyses, only the first five tests are included.

6.2.4.3. Timed Up and Go Test (TUG)

The Timed Up and Go Test (TUG) is designed to assess mobility. It measures the time in seconds for a person to rise from sitting from a standard armchair, walk 3 meters, turn, walk back to the chair, and sit down. The subject wears regular footwear and uses his/her customary walking aid. A score of >15 seconds indicates client has increased risk of falls.

6.2.4.4. Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-GCIC)

The ADCS-GCIC scale consists of a format with which a clinician may address clinically relevant overall change, including 15 areas under the domains of cognition, behavior, and social and daily functioning. The rater, at baseline, interviews the subjects and caregiver/informant, using a form that comprehensively

lists relevant symptoms potentially useful in judging change, and makes notes for future reference. By allowing raters to use the forms in an unstructured manner, this scale may facilitate clinical judgments with face validity. At follow-up visits, the clinician uses a similar set of forms to re-interview the patient and caregiver/informant. The ADCS-GCIC rating is made on a 7-point scale similar to other global change scales, where a higher score indicated marked improvement. The ADCS-GCIC was added to complement the CDR-SB as several domains affects in DLB (e.g., sleep, behavior, fluctuations, motor) are not adequately captured in the 6 CDR domains.

6.2.4.5. Dementia Cognitive Fluctuations Scale (DCFS)

Cognitive fluctuations are common in DLB, are a core symptom in the diagnostic criteria, and contribute significantly to caregiver stress. The DCFS has been validated and shown to detect disease worsening.

6.2.4.6. 12-item Neuro-Psychiatric Inventory (NPI-12)

The NPI-12 is designed to assess psychopathology in the person with dementia and to help distinguish between the different causes of dementia. The NPI-12 examines 12 sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, sleep and night-time behavior change, and appetite and eating change. Of the domains hallucinations are of particular interest as visual hallucinations are present in 80% of patients with dementia with Lewy bodies at presentation.

The NPI-12 is administrated to caregivers of dementia subjects. A screening question is asked about each included sub-domain. If the responses to these questions indicate that the subject has problems with a particular sub-domain of behavior, the caregiver is only then asked all the questions about that domain, rating the frequency of the symptoms on a 4-point scale, their severity on a 3-point scale, and the distress the symptom causes them on a 5-point scale.

6.2.4.7. Movement Disorder Society – Unified Parkinson's Disease Rating Scale – Part III (MSD-UPDRS3)

The MDS-UPDRS3 is a gold standard assessment of Parkinson's disease, with the motor examination evaluating aspects of the disease that are overlapping with features of DLB. The motor examination (Part III) assesses motor symptoms and signs with scores range from 0-108, with higher scores supporting more severe symptoms.

6.2.4.8. Mini-Mental State Examination (MMSE)

The MMSE consists of 11 tests of orientation, memory (recent and immediate), concentration, language, and praxis. Scores range from 0 to 30, with lower scores indicating greater cognitive impairment.

6.2.4.9. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician-administered instrument that assesses suicidal ideation and behavior (Posner et al, 2011). The "Baseline" version of the instrument will be administered to subjects during Screening, and the "Since Last Visit" version will be used at subsequent time points specified in Table 6-1 and Table 6-2. If there is an increased risk for suicidal ideation and behavior, the investigator should refer the subject to a psychiatric doctor or service for additional help and should consider if discontinuation from treatment is recommended.

6.2.5. Physical Examination and Vital Signs

Physical examination will include a review of all body systems and measurement of weight, per each Investigators standard practice. Physical examination findings will be documented in the subject's source documents.

Vital signs include measurement of blood pressure, pulse, respiratory rate, and body temperature. Vital signs are to be measured with the subject in a sitting position after 5 minutes.

Any physical examination finding or vital sign measurement that represents a worsening from Baseline condition and is considered by the Investigator to be clinically significant will be recorded as an AE (see Section 7).

6.2.6. Electroencephalography (EEG)

Quantitative electroencephalography (qEEG) will be performed with the subject awake in accordance with the 10-20 International System of Electrode placement at the time points specified in Table 6-1 according to a standard protocol that will be provided in a separate EEG manual. Slowing of the dominant frequency band by qEEG over posterior aspects of the brain has been recognized to be prominent in DLB (Peraza et al, 2018), and various patterns have been identified to differentiate DLB from AD. EEG has also been recognized to be potential biomarker for DLB in the most recent consensus report of the DLB consortium (McKeith et al, 2017). In addition, alpha reactivity was recently reported (Schumacher et al, 2020; Jennings et al, 2022) as a specific measure for DLB and a measure of "cholinergic integrity" in both DLB and AD. If a site or a can not or will not perform EEG assessments, this does not constitute a deviation and the patient can enroll, and the site can participate without EEG assessments.

6.2.7. 12-Lead Electrocardiogram

A 12-lead ECG will be performed during Screening using validated machinery available locally to each clinical site. ECG parameters to be captured include heart rate (bpm), PR interval, QRS duration, QT interval, corrected QT interval (using Fridericia's formula), and RR interval Each report will be reviewed by the Investigator or qualified sub-investigator and assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant. Abnormal, clinically significant findings are to be reported as part of the subject's medical history.

6.2.8. Clinical Laboratory Assessments

Blood samples will be collected at the time points specified in Table 6-1 and Table 6-2 for assessment of routine chemistry and hematology analytes. Additional blood samples will be collected for coagulation studies at the time points specified in Table 6-1 and Table 6-2.

All samples will be analyzed via a central laboratory. Samples will be destroyed immediately following analysis.

Table 6-3: Clinical Laboratory Analytes

Serum Chemistry

- Albumin
- Alkaline phosphatase
- ALT
- AST
- Bilirubin (total and direct)
- Glucose
- Blood urea nitrogen
- Calcium
- Bicarbonate/Carbon Dioxide
- Chloride
- Total cholesterol
- Triglycerides
- Creatinine
- Gamma-glutamyl transferase
- Lactate dehydrogenase
- Phosphate
- Potassium
- Sodium
- Total protein
- Uric acid

Hematology

- Differential (absolute and percent)
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils
- Erythrocytes
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Hemoglobin
- Leukocytes
- Platelets

Coagulation Studies

- Prothrombin time
- Partial thromboplastin time
- INR

Clinical laboratory findings that represent a worsening from Baseline value and are considered by the Investigator to be clinically significant will be recorded as an AE (refer to Section 7).

6.2.9. Pharmacokinetics (PK)

Blood samples for PK will be obtained at the Week 2 visit in the Treatment Phase and Week 4 in the Extension Phase prior to the morning dose for determination of trough plasma drug concentration as specified in Table 6-1 and Table 6-2. Samples will be analyzed and stored at a central bioanalytical lab until the end of the study and will then be transferred to a biorepository for long term storage (until 2 years after the date of marketing application or discontinuation of the product).

6.2.10. Biomarker Testing

A plasma sample for pTau analysis will be obtained at Screening and evaluated for eligibility purposes. Additional plasma samples for protein biomarker assessment are to be collected at the timepoints specified in Table 6-1 and Table 6-2. Samples will be stored for future protein biomarker testing once applicable assays are identified or developed; note that such samples will not be used for genetic testing.

pTau samples will be analyzed and stored at a central biomarker lab until the end of the study and will then be transferred to a biorepository for long term storage (until 2 years after the date of marketing application or discontinuation of the product).

Biomarker samples will be shipped and stored at the central laboratory until the end of the study and will then be transferred to a biorepository for long term storage and future analysis (until 2 years after the date of marketing application or discontinuation of the product).

6.2.11. Withdrawal of Subjects

A subject may be discontinued from study treatment at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or withdrawal of surrogate consent)
- Subject is not compliant with study procedures
- Protocol violation requiring discontinuation of study treatment
- AE that in the opinion of the Investigator would be in the best interest of the subject to discontinue study treatment
- Subject develops suicidal ideations or attempts suicide
- Subject becomes incapacitated, i.e., loses the capacity to consent due to cognitive decline, in the opinion of the investigator
- Lost to follow-up
- Sponsor request for early termination of study

If a subject is withdrawn from treatment due to an AE, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

A subject may be withdrawn from the study at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the Investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

Refer to the Schedule of Assessments for assessments to be performed for subjects who prematurely discontinue study drug.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS/SAFETY REPORTING

The Investigator is responsible for reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

7.1. Definitions and Criteria

7.1.1. Adverse Events

Per International Council for Harmonisation (ICH) E2A: An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as treatment of the AEs.

7.1.2. Serious Adverse Events

An SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse; malignancy)

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe; e.g., an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours' duration may be rated as severe but may not be considered serious.

The following hospitalizations are not considered serious:

- A visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered 'important medical event' or event life-threatening).
- Elective surgery, planned prior to signing the informed consent form (ICF).
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

7.1.3. Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction (ADR) is a reaction for which the nature or severity is not consistent with the applicable product information (Investigator's Brochure, Package Insert for marketed products). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Guidance on reporting AEs and SAEs is described in Section 7.2.

7.1.4. Abnormal Laboratory Values

Any abnormality in a laboratory value that is new in onset or which has worsened in severity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests.
- Leads to discontinuation of investigational product.
- Has accompanying or inducing symptoms or signs.
- Is judged by the Investigator as clinically significant.

7.1.5. Assessing Intensity and Relationship

All AEs will be assessed on 2 descriptive parameters: intensity and relationship to the investigational product:

- Intensity refers to the severity of an event and references impact on a subject's functioning.

- Relationship refers to the likelihood that the event being assessed was caused by the investigational product.

Intensity

Each AE will be classified according to the following criteria:

Mild:	The AE does not interfere in a significant manner with the subject's normal level of functioning.
Moderate:	The AE produces some impairment of functioning but is not hazardous to the subject's health.
Severe:	The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, those changes should be recorded separately (with distinct onset dates).

Relationship

Each AE will be assessed as to its relationship to the investigational product, based on the following criteria. Although the attribution by the Investigator will be collected for reported events, for analytic purposes a temporal association with the use of the investigational product will be assumed sufficient for at least plausible association.

Not related:	No causal relationship exists between the investigational product and the AE, but an obvious alternative cause exists, e.g., the subject's underlying medical condition or concomitant therapy.
Possibly related:	A connection with the administration of the investigational product appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the investigational product; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the investigational product.
Related:	There is a reasonable/plausible possibility that the AE may have been caused by the investigational product.

When assessing the relationship to the investigational product, the following criteria will be considered:

- Positive rechallenge
- Positive dechallenge (resolution upon stopping suspect the investigational product, in absence of other intervention or treatment)
- Known class effect
- Biological plausibility
- Lack of alternative explanation—concomitant drug or disease

7.2. Reporting Procedures and Requirements

7.2.1. Adverse Events (AE)

AEs occurring from when the subject signs the ICF until the last study event will be recorded. Any AEs occurring before the start of treatment (i.e., before the first dose of the investigational product) will be recorded in the medical history. Also, the sign, symptom, or disease present before starting the treatment period are only considered AEs if they worsen after starting the treatment period.

If the Investigator detects an AE in a study subject after the last scheduled follow-up visit and considers the event possibly related or related to prior study treatment, the Investigator should report it to the Sponsor or designee.

The Investigator should report all AEs on the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term rather than symptoms, (e.g., "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever") and should be described with the attributes described in Section 7.1.5.

7.2.2. Serious Adverse Events (SAE)

Each AE will be assessed to determine whether it meets seriousness criteria (Section 7.1.2). If the AE is considered serious, the Investigator should report this event to the Sponsor or designee as outlined below and also to the IEC according to its standard operating procedures.

The Investigator must report all SAEs **via an eCRF in the EDC system** within 24 hours of learning about the event regardless of relationship to study drug.

If the Investigator/site experiences a temporary disruption of the EDC system, a back-up paper SAE Report Form will be available for Investigator/site staff to complete. If a paper SAE Report Form is utilized, it must follow the same timelines and be emailed or faxed within 24 hours of learning about the event regardless of relationship to study drug.

SAE Reporting:

E-mail: drugsafety@worldwide.com

Fax: +1 866 387-5539 *US) or +44 208 043 4813 (ROW)

If notification is made via email or fax, site staff must enter the SAE information into the EDC system as soon as the system becomes available. Should a paper SAE form be used, the original SAE form should be kept at the site.

Each SAE should be followed up until resolution or stabilization. For reported deaths, the Investigator should supply the Sponsor or designee and the IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

The Sponsor or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IEC of all SAEs that occur at the Investigator's site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial.

SAEs that are ongoing at the Follow-Up Visit should be followed until resolution, until the condition stabilizes, until the subject is lost to follow-up or otherwise explained.

If the Investigator detects an SAE in a study subject after the last scheduled follow-up visit, and considers the SAE related or possibly related to prior study treatment, the Investigator should report it to the Sponsor.

8. DATA MANAGEMENT AND STATISTICAL ANALYSIS

8.1. Data Management and Quality Assurance Considerations

This study will employ eCRFs via an electronic data capture (EDC) system. The site will be trained on specific forms and procedures for source documentation and maintenance of an audit trail of the data that is entered on the eCRF prior to study initiation.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific eCRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by subject number (6 digits: the first 3 for the study center and the last 3 for the subject).

The Investigators will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

If a correction is required for an eCRF, the time and date will be automatically recorded by the EDC system indicating the person updating eCRF data in order to create an audit trail. The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties.

Database lock will occur once quality assurance procedures have been completed.

The statistical analysis of this data will be performed by the Sponsor or designee. All AEs will be coded using the latest version of the Medical Dictionary for Regulated Activities (MedDRA). Concomitant medications will be coded using the latest version of the World Health Organization Drug (WHODrug) Dictionary.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting United States Food and Drug Administration (FDA), European Medicines Agency, and ICH guidelines for the handling and analysis of data for clinical studies. Data management details will be outlined in a separate Data Management Plan.

8.2. Sample Size

The primary hypothesis for the trial is that neflamapimod will significantly improve outcome vs. placebo on the CDR-SB. To demonstrate this effect, a total of approximately 160 subjects are planned to be enrolled, of whom 80 are planned to receive neflamapimod and 80 are planned to receive placebo. Sample size was determined by power analysis via simulations, conducted by utilizing outcomes in the CDR-SB in neflamapimod 40mg TID and placebo groups in the Phase 2a clinical trial in DLB (Study 501), to generate for each patient a change from baseline in the CDR-SB score at individual visits over the course of the simulated clinical study, and then analyzing the result of each clinical trial utilizing the linear mixed effects model for repeated measures that will be utilized to analyze the current study. Based on the simulation of 100 clinical trials with 80 patients per treatment group, and assuming a 10% dropout rate, there is greater than 90% power (95% confidence interval 90 to 99%) to detect a treatment effect at an alpha level of 0.05. Note: in the phase 2a study, the difference in change in CDR-SB between 40mg

TID and placebo from the MMRM analysis was -0.56 (95% confidence interval -0.96,-0.16).Analysis Sets

The safety analysis set will include any subject who receives at least 1 dose of study drug.

The efficacy analysis set will include any subject who receives at least 1 dose of study drug and at least one post-dose cognitive assessment.

Analyses will be fully outlined in a Statistical Analysis Plan finalized prior to the end of enrollment.

8.3. Analysis Sets

The safety analysis set will include any subject who receives at least 1 dose of study drug.

The efficacy analysis set will include any subject who receives at least 1 dose of study drug and at least one post-dose cognitive assessment.

Analyses will be fully outlined in a Statistical Analysis Plan finalized prior to the end of enrollment.

8.4. Safety

The incidence of treatment-emergent AE and SAEs, the causal relationship between an AE/SAE, and the Study Drug and severity will be tabulated by treatment (dose) group.

Individual clinically significant changes in clinical laboratory and ECG parameters will be listed along with median and mean and standard deviation by treatment group.

8.5. Efficacy

The primary efficacy variable is:

- Change in CDR-SB in neflamapimod-treated subjects compared to placebo-recipients.

Secondary efficacy variables are:

- Change in TUG in neflamapimod-treated subjects compared to placebo-recipients.
- Change in the composite score of the Neuropsychological Test Battery (NTB), including assessments of attention, executive function, and visuospatial function in neflamapimod treated-subjects as compared to the placebo-treated subjects.
- ADCS-GCIC at Week 16 in neflamapimod-treated subjects compared to placebo-recipients.

As exploratory efficacy variables, the effects of neflamapimod relative to placebo will be evaluated via:

- Change in Dementia Cognitive Fluctuations Scale (DCFS)
- Select domains of the 12-item Neuropsychiatric Inventory (NPI-12), including depression (dysphoria), apathy, hallucinations, and agitation/aggression.
- Change in hallucinations frequency x severity score within the NPI-12 in subjects who report hallucinations at baseline.

- Change in sleep and night-time behavior change within the NPI-12.
- Change in MDS-UPDRS3 motor examination (Part III) score
- Change in beta functional connectivity and in alpha reactivity on quantitative EEG.

The primary endpoint will be analyzed using the Mixed Effects Model for Repeated Measures (MMRM) analysis method with the change from baseline in the CDR-SB as the dependent variable and will use an unstructured covariance matrix. This analysis will be performed on the efficacy analysis population, which will include all subjects who receive at least one dose of study drug and provide at least one post-dose cognitive assessment. Additional covariates to be included in the MMRM model will be provided in the Statistical Analysis Plan (SAP) which will be finalized prior to the end of enrollment. Further descriptions of sensitivity analyses, as well as any additional efficacy populations that may be used to assess efficacy will also be provided in the SAP. The TUG and NTB endpoints will also be analyzed using MMRM analysis method, though the model may be adapted to the specific endpoints (defined by SAP). For the NTB, a primary composite z-scores will be calculated and used in order to create standardized change scores to be used for the analysis. Additionally, sensitivity analyses will be performed on the primary endpoint specifically to address different missing data scenarios, both Missing at Random and Missing Not at Random. ADCS-CGIC at Week 16 in neflamapimod vs. placebo will be compared utilizing a two-sided Mann Whitney test. The primary and secondary endpoints, including the primary and secondary EEG endpoints, will be assessed for statistical significance at p-value of 0.05. Exploratory endpoints will not be tested for significance, but presented with treatment effect vs. placebo, with 95% confidence intervals. Other analyses, including the approach to analyzing exploratory endpoints will be included in the SAP.

8.6. Interim Analysis

No interim analysis is planned. The primary analyses will be performed after the blinded treatment period of 16 weeks. Patients may go on to a long term open-label extension and a final analysis will be performed with the additional long-term data.

9. STUDY MANAGEMENT

9.1. Ethics and Consent

9.1.1. Regulations and Guidelines

The study will be performed in accordance with this protocol, United States Investigational New Drug Application regulations (21 CFR 312) or local national laws (as applicable) and ICH guidelines for Good Clinical Practice.

9.1.2. Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC. Approval is required for the study protocol, investigational drug brochure, protocol amendments, ICFs, subject information sheets, and advertising materials. No investigational product will be shipped to a site until written IEC authorization has been received by the Sponsor or its designee.

9.1.3. Informed Consent

For each study subject, written informed consent must be obtained from the subject before the performance of any protocol-related activities. As part of this procedure, the Investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the investigational product in such a manner that the subject is aware of the potential risks, inconveniences, or adverse effects that may occur. Subjects should be informed that they may withdraw from the study at any time. They will receive all information that is required by local regulations and ICH guidelines. The Investigator or a designated representative will provide the Sponsor or its designee with a copy of the IEC-approved ICF before the start of the study.

9.2. Indemnification

The Sponsor's indemnification of the Investigator and institution during the conduct of this study is addressed in a letter of indemnification provided as a separate document. Other indemnification or insurance will be provided as necessary under local regulations.

9.3. Discontinuation of the Study by the Sponsor

The planned study period is approximately 2 years, until the last visit of the last subject (including the follow-up visit). The planned subject participation is up to 23 weeks, including 16 weeks of treatment. Once the subjects have ended their participation in the study, they can return to their standard of care treatment as determined by their physician. Subjects who complete the 16-week treatment phase will also be offered the opportunity to continue in a 32-week open-label extension phase.

If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then this can happen only after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant study termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- Failure of the Investigator to enter subjects at an acceptable rate.

- Unsatisfactory subject enrollment with respect to quality and/or quantity or data recording is inaccurate and/or incomplete on a chronic basis.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of study drug.

Should the study be terminated and/or the site closed for whatever reason, all documentation and investigational product pertaining to the study must be returned to the Sponsor or its designee.

9.4. Study Documentation

By signing a copy of Form FDA 1572 or other country-specific regulatory forms, the Investigator acknowledges that he/she has received a copy of the IB on neflamapimod and assures the Sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572 and other country-specific forms. No changes in this protocol can be made without the Sponsor's written approval.

9.5. Study Monitoring and Auditing

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the Sponsor or its designee. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to the protocol, standard operating procedures, Guidelines of Good Clinical Practice, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

9.6. Use of Study Findings

By signing the study protocol, the Investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its designee.

9.7. Publications

The clinical study will be registered at www.clinicaltrials.gov and www.clinicaltrialsregister.eu. The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws.

9.8. Recording, Access and Retention of Source Data

The Investigators must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee) and Regulatory Agency inspectors upon request.

A file for each subject must be maintained that includes the signed Informed Consent and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

All study documents (subject files, signed ICFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

9.9. Protocol Violations

A protocol violation occurs when the subject, Investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety, and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the Investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

9.10. Data and Safety Monitoring Board (DSMB)

There will be a Data and Safety Monitoring Board (DSMB) responsible for overseeing the safety of human subjects in this clinical trial. The DSMB will include at least three (3) members: two (2) clinicians with experience with dementia clinical trials, one of which will be the chair, and one (1) statistician. Members of the DSMB will be separate from the study team and site teams. The DSMB Charter will be reviewed and adopted by the DSMB; it will be a standalone document.

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